

PATENT

PATENT APPLICATION

Genetic Analysis Systems and Methods

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New Utility Patent Application

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Genetic Analysis Systems and Methods

BACKGROUND OF THE INVENTION

The DNA that makes up human chromosomes provides the instructions that direct the production of all proteins in the body. These proteins carry out the vital functions of life. Variations in DNA often produce variations in the proteins, thus affecting the function of cells. Although environment often plays a significant role, variations or mutations in DNA are directly related to almost all human diseases, including infectious disease, cancer, inherited disorders, and autoimmune disorders. Moreover, knowledge of human genetics has led to the realization that many diseases result from either complex interactions of several genes or from any number of mutations within one gene. For example, Type I and II diabetes have been linked to multiple genes, each with its own pattern of mutations. In contrast, cystic fibrosis can be caused by any one of over 300 different mutations in a single gene.

Additionally, knowledge of human genetics has led to a limited understanding of differences between individuals when it comes to drug response—the field of pharmacogenetics. Since the first correlation over half a century ago of adverse drug responses with amino acid variations in two drug-metabolizing enzymes, plasma cholinesterase and glucose-6-phosphate dehydrogenase, careful genetic analyses have linked sequence polymorphisms in over 35 drug metabolism enzymes, 25 drug targets and 5 drug transporters with compromised levels of drug efficacy or safety. In the clinic, such information is being used to prevent drug toxicities; for example, patients are often screened for genetic differences in the thiopurine methyltransferase gene that cause decreased metabolism of 6-mercaptopurine or azathiopurine. Yet only a small percentage of observed drug toxicities have been explained adequately by the set of pharmacogenetic markers validated to date. In addition, insufficient therapeutic efficacy or unanticipated side effects in "outlier" individuals when administered drugs previously demonstrated to be both safe and efficacious in clinical trials is a tremendous problem for health care practitioners and presents a significant dilemma to the pharmaceutical industry.

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Disease-related and pharmacogenetic gene validation relies on elements of population and quantitative genetics and robust statistical metrics; however, the first step normally relies upon identification of a candidate target gene. To date, various biotechnological methods have been employed to identify candidate genes. For example, differential gene expression has been employed, essentially looking for differences in gene expression between affected and unaffected individuals or between treated and untreated individuals. In addition, protein-protein interaction maps to identify drug receptors and their immediate effectors have been used. Another approach involves mining human sequence databases for sequences similar to accepted disease-related or pharmacokinetic or pharmacodynamic regulators.

Because any two humans are 99.9% similar in their genetic makeup, most of the sequence of the DNA of their genomes is identical. However, there are variations in DNA sequence between individuals. For example, there are deletions of many-base stretches of DNA, insertion of stretches of DNA, variations in the number of repetitive DNA elements in noncoding regions, and changes in single nitrogenous base positions in the genome called "single nucleotide polymorphisms" or "SNPs". It is estimated that there are 3 to 4 million common SNPs that occur in at least 10 percent of people. These common SNPs do not occur independently but are passed from generation to generation in variable-length blocks of multiple SNPs, forming patterns across the genome. Such blocks of SNPs are called SNP haplotype blocks herein.

The candidate gene identification strategy most relevant to SNPs is whole-genome association on various populations of individuals—that is, scanning the entire genomes of populations of individuals to correlate SNPs to disease or drug response. Such whole-genome analyses would provide a fine degree of genetic mapping and pinpoint specific regions of linkage. Methods have been proposed and are used in connection with whole genome analysis. For example, the methods described in U.S. Ser. No. 60/327,006, filed October 5, 2001, "Identifying Human SNP Haplotypes, Informative SNPs and Uses Thereof," assigned to the assignee of the present invention (Attorney docket no. 054801-5001-P2; 1005-P3, incorporated herein by reference for all purposes) have been proposed

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for use in such applications. U.S. Ser. No. unassigned, filed September 18, 2001, "Human Genomic Polymorphisms", assigned to the assignee of the present invention (Attorney Docket no. 10108319/1013P-1) incorporated herein by reference for all purposes, provides the identity of SNPs and SNP haplotype blocks across one representative chromosome, ie. Chromosome 21.

While meeting with success, it is desirable to increase the speed and efficiency at which such analyses can be performed, as well as to decrease the cost of performing such analyses.

SUMMARY OF THE INVENTION

Improved methods, devices, and systems for performing genetic analysis are provided. According to one embodiment of the invention a method is provided in which genetic DNA or derivatives therefrom is scanned from a plurality of individuals. The scanning uses, for example, a gel based sequencer or high density array to identify genetic polymorphisms in a plurality of individuals. For the polymorphisms that occur in a plurality of individuals, but not all of the scanned bases, genetic DNA or derivatives therefrom from additional individuals is evaluated to identify which of the variants occur in the additional individuals. Based the results of scanning the additional individuals, the method provides for the identification of blocks of the polymorphisms that tend to be inherited together. The blocks of polymorphisms can then be used in a wide variety of applications such as drug target identification, identification of diagnostics, clinical trial evaluation, pharmacogenomics, and other applications.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Throughout the disclosure various patents, patent applications and publications are referenced. Unless otherwise indicated, each is incorporated by reference in its entirety for all purposes.

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U.S. Ser. No. 60/327,006, filed October 5, 2001, "Identifying Human SNP Haplotypes, Informative SNPs and Use Thereof," assigned to the assignee of the present invention (Attorney docket no. 054801-5001-P2) incorporated herein by reference for all purposes, describes methods for identifying single nucleotide polymorphisms, assigning such polymorphisms to groups, and using such groups in the drug discovery process. Fig. 1 provides an overall diagram illustrating such processes. In Fig. 1, variant locations in a genome, such as the human genome, are identified in step 110. The processes used in step 110 can include, for example, scanning genomic regions for variants using DNA/RNA arrays such as those available from Affymetrix, Inc. (such as discussed in general in U.S. Pat. No. 5,861,242, incorporated herein by reference for all purposes), the use of conventional gel sequencing techniques such as those based on gel sequencers available from Applied Biosystems, Inc., capillary sequencing techniques, or other techniques. Preferably, only common SNPs, such as those that occur in more than 10% of the population in question, are used in the analysis since, for example, these SNPs will represent evolutionarily older variants and, therefore, tend to correlate with more common diseases/states in a larger fraction of the population.

In preferred embodiments, the genomic DNA (or a derivative therefrom, such as PCR DNAs or RNA amplicons or the like) is scanned for variants using a high density DNA array. Using one technology, an array of probes is formed on a high density array. The array of probes includes a) probes that are complementary to portions of a baseline sequence of the genetic DNA (such as that obtained from a first pass sequencing effort) and b) one or more probes that are complementary to variants of the baseline sequence of the genetic DNA. The genetic DNA, or a derivative thereof, is then labeled and hybridized to the array and scanned. Based on the locations where hybridization is detected one can detect whether the bases in the genetic DNA are "wild type" or variant. In the cases where the particular base is the same as the reference sequence, the labeled material will hybridize more strongly to the wild type probe. In those cases where the DNA sequence varies from the reference sequence, the labeled material will hybridize

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more strongly to one of the variant probes. Based on this information, one can call a particular base as being the same or variant from the reference sequence.

In preferred embodiments, more than 10,000 bases are scanned for variants. In more preferred embodiments, more than 1x106 bases are scanned for variants, more preferably more than $2x10^6$ bases, more preferably $1x10^7$, and more preferably more than $1x10^8$, and more preferably more than $1x10^9$ bases are scanned for variants. In preferred embodiments at least introns are scanned for variants, and in more preferred embodiments both introns and exons are scanned for variants. In preferred embodiments the scanned nucleic acids are genomic DNA. In most preferred embodiments, such DNA is from a mammalian organism such as a human. In preferred embodiments, more than 10% of the genomic DNA from the organism is scanned, in more preferred embodiments more than 25% of the genomic DNA from the organism is scanned, in more preferred embodiments, more than 50% of the genomic DNA from the organism is scanned, and in most preferred embodiments, more than 75% of the genomic DNA is scanned.

In step 120 the variants are assigned to groups. Such groups of variants are blocks of variants (in most cases, single nucleotide polymorphisms or "SNPs") that tend to be inherited together. Such "blocks" or "SNP variant haplotype blocks" have likely arisen from an evolutionary point of view because the edges of blocks will tend to be the boundaries of ancient recombination events in the species. In step 130, representative variants from each block are used in an association study to identify associations of such Such association studies may be run using a variety of blocks to a phenotype. technologies such as a) Affymetrix genotyping arrays, b) "Invader" assays available from Third Wave, such as described in Agarwal, P. et al. "Comparison study for identifying promoter allelic polymorphism in interleukin 10 and tumor necrosis factor alpha genes", Diagn Mol Pathol 9, 158-64(2000); Cooksey, R.C., Holloway, B.P., Oldenburg, M.C., Listenbee, S. & Miller, C.W. "Evaluation of the Invader assay, a linear signal amplification method, for identification of mutations associated with resistance to rifampin and isoniazid in Mycobacterium tuberculosis" Antimicrob Agents Chemother 44, 1296-301 (2000); and Mein, C.A. et al. "Evaluation of single nucleotide polymorphism

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typing with Invader on PCR amplicons and its automation" *Genome Res* 10, 330-43 (2000), all incorporated herein by reference, or c) "Taqman" assays, such as described in Arnold, B.A., Hepler, R.W., and Keller, P.M. "One-Step Fluorescent Probe Product-Enhanced Reverse Transcriptase Assay" *BioTechniques* 25(1):98-106, 1998; Becker K., D. Pan and C.B. Whitley. 1999. Real-time quantitative polymerase chain reaction to assess gene transfer. Hum. Gene Ther. 10:2559-2566, 1999; Berg, T., Miller, A.R., Platz, K.P., Hohne, M., Bechstein, W.O., Hopf, U., Wiedenmann, B., Neuhaus, P., and Schreier, E. "Dynamics of GB virus C viremia early after orthotopic liver transplantation indicates extrahepatic tissues as the predominant site of GB virus C replication" *Hepatology* 29(1):245-249, 1999; or a variety of other technologies. When array based technologies are used, as an example, one makes arrays similar to those described above, except that only the variant positions are "tiled" onto the array.

Once it has been determined which regions of the genome are associated with, for example, a disease state, drug screening assays are run to identify one or more molecules that mediate the relevant portions of the genome in step 140 to identify therapeutics 150. In addition, the associations themselves may be used directly in genetic diagnostic assays, immunoassays or other diagnostic tests in step 160. In alternative embodiments the variant regions are used in studies to evaluate drug response such as in pharmacogenomic studies. The results are then used to stratify patents according to drug response. The stratification may, in some embodiments, be used to stratify individuals that may exhibit a toxic response from those that will not. In other cases, the stratification may separate those that will be non-responders from those who will be responders.

Fig. 2 provides one illustration of showing how variants, usually SNPs, occur in groups or blocks in a genome. Such SNP haplotype blocks are chromosomal regions that tend to be inherited as a unit, with a relatively small number of common forms. Each line in Fig. 2 represents portions of the haploid genome sequence of different individuals. As shown therein, individual W has an "A" at position 241, a "G" at position 242, and an "A" at position 243. Individual X has the same bases at positions 241, 242, and 243. Conversely, individual Y has a T at positions 241 and 243, but an A at position 242.

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Individual Z has the same bases as individual Y at positions 241, 242, and 243. The variants will most commonly be biallelic, ie. occur in only one of 2 forms, not all four possibilities. Variants in block 261 will tend to occur together. Similarly, the variants in blocks 262 and 263 will tend to occur together. Of course, only a few bases in a genome are shown in Fig. 2. In fact, most bases will be like those at position 245 and 248, and will not vary from individual to individual.

This tendency of SNPs to occur together in SNP haplotype blocks allows for a single or a few SNPs in a block to be used in an association study, rather than all of the SNPs in that block. For example, by evaluating only the SNP at position 241, the SNPs at positions 242 and 243 can be predicted without performing an assay to identify SNPs 242 and 243. If position 241 contains an A, position 242 will contain a G and position 243 will contain an A. Conversely, if position 241 contains a T, positions 242 and 243 respectively will contain an A and a T respectively. Similarly, a SNP in block 262 can be used to predict the other SNPs in block 262. For example, if SNP 244 is a T, it will be known that position 246 is a C, and position 247 is a G. Conversely, if position 244 is a C, position 246 is an A, and position 247 is a C.

According to the invention herein, all or substantially all of the bases in a genomic region are scanned for common SNPs in a first, limited, sample set. Then, using substantially only those SNPs identified in the first scanning step, additional individuals are genotyped at those SNP locations that are identified from a full scan of the genomic region of interest. The first sample set is sufficiently large that the full scan of genomic DNA identifies a sufficient number of SNPs with a sufficiently high level of confidence, but is not large enough to necessarily identify all of the block boundaries to a necessary level of confidence for the particular experiment. The second sample set is of a sufficient size that it will allow definition of block boundaries with a sufficient level of confidence for the experiment.

Fig. 3 illustrates the process in greater detail. As shown, at step 310 a subset of "n" genomic DNAs are scanned across all or a portion such genomes at every base location for common SNPs or variants. Thereafter, using genotyping technologies such

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as those described above, only those variant locations identified in step 310 are used to genotype an additional "m" individuals. Using the genotypes accumulated from steps 310 and 320, variant blocks are assigned. Using the invention herein, the cost and burden of performing genetic analysis, especially whole genome analysis, is significantly reduced since, for a fraction of the population analyzed, only a fraction of the bases of the genomic DNA of interest needs to be evaluated in assigning variants to respective blocks.

In preferred embodiments, copies of more than 10 different monoploid genomic DNAs are scanned for variants at step 310 to be used in the further genotyping analysis (i.e. "n" is 10 or more). In more preferred embodiments more than 15 different copies of the genomic DNA are scanned for variants to be used in the further genotyping analysis (i.e. "n" is 15 or more). In more preferred embodiments more than 18 copies of the genomic DNA are scanned for variants to be used in the further genotyping analysis (i.e. "n" is 18 or more). In more preferred embodiments more than 20 genomic DNAs are scanned for variants to be used in the further genotyping analysis (i.e. "n" is 20 or more). In more preferred embodiments more than 25 copies of the genomic DNA are scanned for variants to be used in the further genotyping analysis (i.e. "n" is 25 or more).

In preferred embodiments, the full scanning of genomic DNA is followed up by genotyping at step 320 of additional samples to evaluate representative SNPs discovered in the full scans. In preferred embodiments, the genotyping step 320 analyzes more than 10 different monoploid genomic DNAs (ie. "m" is 10 or more). In more preferred embodiments, the genotyping step 320 analyzes more than 15 different genomic DNAs. In more preferred embodiments, the genotyping step 320 analyzes more than 20 different genomic DNAs. In more preferred embodiments, the genotyping step 320 analyzes more than 25 different genomic DNAs. In more preferred embodiments, the genotyping step 320 analyzes more than 30 different genomic DNAs.

Fig. 4 illustrates the outcome of the process of Fig. 3 in a hypothetical situation. The top portion of Fig. 4 illustrates the sequence of a hypothetical stretch of DNA, with the variant positions indicated and variant block boundaries drawn. Of course, the top portion of Fig. 4 illustrates the stretch of genomic DNA with mutations marked and the

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block boundaries drawn, although this information would not be known ab initio. Sequencing results 410 show the results of sequencing haploid DNA of 3 individuals. As shown, in general it is possible to have identified a large fraction of the common SNPs after a relatively small number of individuals have been sequenced. In the case in Fig. 4, the SNPs at each location shown in the top portion of Fig. 4 have been identified, as indicated by check marks. However, if further individuals are not evaluated, the block boundaries would not be correctly identified at this stage. For example, while one could at this stage draw block boundaries between blocks 420 and 430 (note that the first $C \rightarrow G$ variant predicts the first $G \rightarrow A$ variant, and the first $C \rightarrow T$ variant predicts the second $C \rightarrow T$ variant), it is not possible to distinguish between the blocks 430 and 440 at this stage. At this stage it appears that the first $C \rightarrow T$ variant would predict the first and second $T \rightarrow A$ variants. Accordingly, a more statistically significant sample set is required to draw the block boundaries. However, since relevant SNPs have been identified, it is now possible to genotype only the variant positions to complete the process of identifying block boundaries without sequencing the entire stretch of genomic DNA.

The results of performing a genotyping process on only the SNPs in another hypothetical genomic sample are shown in Fig. 4 at 420. As shown, by performing this additional genotyping step, it is now possible to see that blocks 430 and 440 are distinguishable. Specifically, it is now possible to see that the first $C \rightarrow T$ variant does not track with the first and second $T \rightarrow A$ variants, but instead, the first $C \rightarrow T$ variant can be used to predict only the second $C \rightarrow T$ variant and the first $T \rightarrow A$ variant can be used only to predict the second $T \rightarrow A$ variant.

Without wishing to be bound by any particular theory of operation, it is believed that the basis on which the assays may be successfully utilized in this manner is found in the fact that a few individuals may be used to find the most common SNPs. The most common haplotypes account for most individuals, but less common haplotypes could be mis-ordered in terms of frequency of occurrence if a larger sample set is not used.

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Example(s)

Using Affymetrix whole wafers, a region of genomic DNA from chromosome 21 was scanned for polymorphic regions, generally using the methods of U.S. Ser. No. 60/327,006, filed October 5, 2001, "Identifying Human SNP Haplotypes, Informative SNPs and Use Thereof," assigned to the assignee of the present invention (Attorney docket no. 054801-5001-P2; 1005-P3, incorporated herein by reference for all purposes). 19 additional copies of chromosome 21 were then evaluated using the same techniques. "Common" SNPs were evaluated, meaning those that occur with an allele frequency of more than 10% in this particular example. To evaluate whether one may use 19 scans for SNP detection, rather than 38, it was determined how many SNPs would produce an allele frequency of >10% across all 38 scans, but are not considered common polymorphism in a set of just 19 scans. To have an allele frequency of >10% out of 38, a SNP would need to have a frequency of >20% in 19 scans, if it is not polymorphic at all in the other 19 scans. In the analysis performed, 89% of common SNPs were identified by evaluating just 19 scans. SNPs identified in the above analysis are shown in Tables 1, 2, and 3. Table 1 shows the SNPs that would have been found in both of the first and last 19 scans of a 38 scan set. Table 2 shows the SNPs that would have been identified by evaluating the first 19 of the 38 scans of chromosome 21, but would not have been identified by evaluating only the second 19 scans. Table 3 shows the SNPs that would have been identified by evaluating the last 19 of 38 scans of chromosome 21, but would not have been identified by evaluating only the first 19 scans. There are 3170 SNPs identified in both the first and last 19 scans. There are 361 SNPs found in only the first Therefore, there are ((0.5))19 scans, and 516 in only the second 19 scans. (361+516))/(3170+361+516) or 11% of the SNPs, on average, that would not be found in only half of the number of scans in chromosome 21.



		POSITION	REFERENCE_BASE	ALTERNATE_BASE
		1: 13780263	a	g
	5	2: 13780367	C	t
	5	3: 13780384	g	a
		4: 13781532	a	g
		5: 13782288	t	C
		6: 13782368	t	С
	10	7: 13787259	t	С
	10	8: 13788521	t	С
		9: 13790624	g	a
		10: 13793189	c	a
		11: 13793483	t	С
l_£	15	12: 13793851	t	С
		13: 13793902	С	a
<u></u>		14: 13793923	a	g
		15: 13794104	g	С
-ţ-		16: 13794163	t	C '
N	20	17: 13794309	a	С
Ö		18: 13794556	g	t
<u></u>		19: 13795184	C	g
d		20: 13795310	a	g
		21: 13796245	С	t
	25	22: 13797171	а	g
		23: 13798473	a	t
		24: 13798594	С	t
		25: 13799031	a	t
ا ا		26: 13799116	a	g
**************************************	30	27: 13799679	a	g
<u> </u>		28: 13799935	g	a
IJ		29: 13800043	g	t
		30: 13800201	a	g
		31: 13800956	t	C
	35	32: 13801272	С	t
		33: 13801560	С	g
		34: 13804651	C	t
		35: 13805013	g	a +
		36: 13805107	С	t t
	40	37: 13805416	С	a
		38: 13805691	g	C
		39: 13806436	t	c
		40: 13808142	g t	c
	15	41: 13808771 42: 13808776		t
	45		C	a
		43: 13808906 44: 13809243	g t	g
		45: 13809448	g	a
		46: 13809729	C	g
	50	47: 13809964	c	t
	50	48: 13810532	a	g
		49: 13811589	g	c
		50: 13812436	g	С
		51: 13829193	a	g
	55	52: 13837787	С	a
	22	53: 13843201	g	t
		54: 13843560	c	t

	55: 13844156 56: 13845008	a g	g C
	57: 13850206	g	t
	58: 13850467	a	t
5	59: 13850793	g	С
	60: 13851331	g	a
	61: 13851465	t	C
	62: 13851482	g	a
10	63: 13851839 64: 13853325	a t	t g
	64: 13853325 65: 13854406	t	C
	66: 13855468	g	a
	67: 13857664	g	а
15	68: 13859884	g	С
	69: 13861361	t	C
	70: 13862014	g	c c
	71: 13862811 72: 13864035	a C	t
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<u>_</u>	74: 13865342	C	t
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<u>II</u>	76: 13870959	a	t
}	77: 13870981	a	g
₫ 25	78: 13872382	a	g t
1 30 30 TO	79: 13872723	a a	g
	80: 13874188 81: 13875913	a	g
	82: 13876910	a	g
□ 30	83: 13877368	t	а
74 J	84: 13877712	g	а
C	85: 13877854	t	C
N	86: 13880011	С	t a
	87: 13880770	g	t
35	88: 13883076 89: 13883341	c t	g
	90: 13883511	a	g
	91: 13883719	C	t
	92: 13884172	g	a
40	93: 13884439	a	g t
	94: 13884476	c c	t
	95: 13885037 96: 13888038	a	t
	97: 13888604	g	t
45	98: 13889436	t	С
	99: 13890344	g	а
	100: 13890511	g	a +
	101: 13891102	a	t g
50	102: 13891894 103: 13891974	a	a
50	103: 13891974 104: 13892019	g t	C
	105: 13892406	a	t
	106: 13892423	а	g
	107: 13892460	С	a
55	108: 13892533	C	t
	109: 13892640	t	c a
	110: 13894072 111: 13894132	g C	a
	111: 13894132 112: 13894680	a	g

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		113:	13895433	ā	a
		114: 115:	13901024 13902432	t t	g g
		116:	13902432	C	g
	5	117:	13904140	g	a
		118:	13905359	c	t
		119:	13906874	a	g
		120:	13908702	t	g
	10	121:	13923816	a	g
	10	122: 123:	13924410 13928582	g	c a
		123: 124:	13929302	g g	a
		125:	13932906	g	a
		126:	13934231	a	С
	15				
		127:	13934282	t	C
		128:	13934468	t	C
		129: 130:	13934480 13934691	a t	C
	20	131:	13936168	t	C
Ţ	20	132:	13939719	g	t
Į.		133:	13945313	g	С
Ð		134:	13945619	t	С
L	2.5	135:	13946328	t	С
'n	25	136:	13948558	t	C
		137:	13957861 13957897	t	C
		138: 139:	13957697	a t	g c
tud La	-	140:	13961398	a	c
H	30	141:	13963166	t	а
÷ i		142:	13963226	a	g
, T-1		143:	13964526	t	g
!		144:	13965988	a	С
H	25	145:	13967031	a	g C
	35	146: 147:	13967361 13968052	a C	g
		148:	13968186	a	g
		149:	13968704	t	g
		150:	13968772	g	а
	40	151:	13969447	C	g
		152:	13969802	t +	g a
		153: 154:	13969816 13969885	t g	a
		155:	13969965	a	C
	45	156:	13970342	t	C
		157:	13971387	t	а
		158:	13971823	С	t
		159:	13983563	g	a
	50	160: 161:	13985003 13985280	a t	g g
	30	162:	13985454	g	a
		163:		a	C
		164:		t	С
		165:	13987607	a	g
	55	166:		C	t
		167:		t	C
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		169: 170:		a	g
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5	171: 13991288 172: 13992670 173: 13992705 174: 13994022 175: 13996917 176: 13997836 177: 13998686 178: 13998835	a t c c t g t g	gcttccaa
10	179: 13999356 180: 14018678 181: 14018887 182: 14019896 183: 14024121	t a t c g	a c g t a
15 <u>-</u>	184: 14024187 185: 14024852 186: 14024923 187: 14028090 188: 14028399	a c a g c	t g t a t
□ □ 20	189: 14028430 190: 14029873	g g	a a
20 F N M 25 U	191: 14031210 192: 14032972 193: 14033384 194: 14034385 195: 14038441 196: 14038480	g c t g a	t t a a c g
5 5 30 5 7	197: 14038639 198: 14040439 199: 14040876 200: 14041428 201: 14041932 202: 14043266	t c g c a c	c g a t g t
O N 35	203: 14044634 204: 14045104 205: 14045200 206: 14048027 207: 14048350 208: 14049343	a a a c c g	g g t t
40	209: 14050138 210: 14050258 211: 14051897 212: 14052199 213: 14053863	g g c c a	a t t
45	214: 14055606 215: 14055656 216: 14056221 217: 14056375 218: 14056470	g a a g c	t g c t
50	219: 14057430 220: 14059144 221: 14060584 222: 14060804	t c t g c	t 0
55	223: 14061225 224: 14064737 225: 14067569 226: 14068069 227: 14068127 228: 14069638	t a a t t	6 (4

5	229: 14070973 230: 14072067 231: 14078398 232: 14079489 233: 14080941 234: 14082287 235: 14082513 236: 14083192	t a g c a g a t	c t a t c a g g g
10	237: 14083520 238: 14087424 239: 14087441	t t g	c a a
	240: 14088548 241: 14091100 242: 14092256	g c	a g t
15	243: 14093151 244: 14094373 245: 14096443	c t g	g c t
⊭ □ □ 20	246: 14097696 247: 14098656 248: 14101014	g a g	a c t
□ 20 ∓ N	249: 14102964	g	a g
Ŋ	250: 14105489 251: 14105717	a C	t
O	252: 14106349	t	g
₩ 25 ₩	253: 14106571 254: 14106827	t g	c a
j	255: 14106974	t	C
	256: 14108664	c c	t g
30	257: 14108889 258: 14109194	C	ť
# 30 T	259: 14109540	a	g
	260: 14109875	a t	g C
N 35	261: 14109953 262: 14109982	t	c
33	263: 14110042	C	t
	264: 14110270	C	t c
	265: 14110383 266: 14110462	t c	t
40	267: 14110527	c	а
	268: 14112293	t	g t
	269: 14112571 270: 14114928	C C	t
	270: 14114326	a	g
45	272: 14116560	g	a g
	273: 14117021 274: 14117699	a g	C
	275: 14117814	a	g
	276: 14118003	a	g C
50	277: 14118769 278: 14121320	t a	g
	279: 14121579	t	С
	280: 14121866	t	g C
55	281: 14122772 282: 14122865	t a	g
33	283: 14124291	a	g
	284: 14124472	C	t C
	285: 14124593 286: 14125680	g t	C
	700: T4T72000	C	

		287: 14129043	a	g
		288: 14129176	C	g
		289: 14130516	g	а
	~	290: 14130838	t	C
	5	291: 14131390 292: 14131972	a C	c t
		292: 14131972 293: 14132126	t	C
		294: 14132401	a	g
		295: 14134814	t	С
	10	296: 14135469	a	g
		297: 14136092	a	c g
		298: 14136237 299: 14136296	a C	t
		300: 14136795	t	С
,	15	301: 14136889	a	g
,		302: 14137167	С	t
ļ.		303: 14137397	a	g a
		304: 14137990 305: 14138306	g g	a
	20	306: 14140410	t	С
1	_0	307: 14140637	g	а
T.J		308: 14140847	а	g
ũ		309: 14140940	C	t t
į	25	310: 14142190 311: 14143299	c g	a
O	23	312: 14148398	t	C
≇ .		313: 14148765	а	t
		314: 14149402	g	С
	20	315: 14150692	t	c t
	30	316: 14150844 317: 14151614	c t	C
, J		318: 14151757	t	a
y De		310. 111111		
N		319: 14152283	С	a
	35	320: 14152410	C	a
		321: 14152443 322: 14152519	a a	g g
		323: 14153887	t	g
		324: 14154251	g	t
	40	325: 14154271	a	g
		326: 14154689	a t	g
		327: 14154783 328: 14154976	a	t
		329: 14155259	c	t
	45	330: 14155374	С	t
		331: 14155524	С	ç
		332: 14155638	g	ŧ
		333: 14156729 334: 14157020	c g	á
	50	335: 14157103	a	ç
	50	336: 14158286	t	C
		337: 14162213	g	(
		338: 14164467	C	Ţ
	55	339: 14166866 340: 14167915	a g	á
	55	341: 14170156	g	á
		342: 14173042	a	ç
		343: 14173477	C	1
		344: 14174757	t	(

		345:	141765		C	t
		346:	141767		t	С
		347:	141769		g	a
	5	348:	141771		g	a
	5	349:	141815 141822		g	a t
		350: 351:	141823		C	t
		352:	141843		g	a
		353:	141848		g	a
	10	354:	141859		g t	c
	10	355:	141860		a	g
		356:	141881		a	g
		357:	141908		t	g
		358:	141924		a	g
	15	359:	141935		t	С
		360:	141943	89	g	a
14		361:	141981	73	C	g
		362:	142012		a	g
F	••	363:	142026		t	С
#==	20	364:	142030		t	C
		365:	142032		a	ā
14		366:	142035		С	t
W		367:	142037		a	c a
1	25	368:	142039 142048		g	a
H	23	369: 370:	142048		g c	t
æ		370:	142076		g	a
		372:	142077		C	t
ļ.		373:	142078		a	g
,	30	374:	142082		a	t
122221 12. 1		375:	142083		t	С
y Chi		376:	142084		С	t
<u></u>		377:	142085	30	t	C
N		378:	142086		С	t
	35	379:	142087		t	а
		380:	142087		С	t
		381:	142090		С	t
		382:	142090	020	a	t
	40	383:	142092		С	t
		384:	142096		t	С
		385:	142097		t	C
		386:			a	C
	15	387:	142115		C	t a
	45	388:	142124 142145		g	C
		389: 390:	142143		g t	C
		391:	142146		g	a
		392:	142185		a	g
	50	393:	142186		a	t
	50	394:	142210		a	g
		395:	14221		a	g
		396:	142212		g	a
		397:	142214	430	ā	g
	55	398:	14221		С	t
		399:	142249	920	g	а
		400:	142282		g	С
		401:			С	t
		402:	14230	581	а	С

	403: 14232644	t	a
	404: 14233411	С	а
	405: 14234037	t	С
	406: 14234266	g	а
5	407: 14235064	С	a
	408: 14235204	С	t
	409: 14235402	g	a
	410: 14235813	С	t
	411: 14236459	а	g
10	412: 14236901	g	a
	413: 14236906	a	c t
	414: 14236958	g	t
	415: 14237106	C	g
15	416: 14237734 417: 14238131	a	a
15		g g	a
	418: 14238784 419: 14238979	a a	t
ļas 	420: 14239101	c	t
	421: 14239346	t	С
₽ 20	422: 14239458	g	а
으 5 20 루 지	423: 14239594	a	g
ħ!	424: 14239790	t	g
	425: 14239876	t	C
to the second	426: 14240218	С	t
<u>1</u> 25	427: 14240377	t	а
a 23	428: 14240473	а	g
≋ .	429: 14241088	а	g
	430: 14241702	а	g
	431: 14241849	g	a
<u> </u>	432: 14242333	С	t
<u>~</u> 1	433: 14243007	a	t
74	434: 14243211	g	C
ted par	435: 14248044	a	C
NJ 25	436: 14249184	C ~	g g
35	437: 14251286	g	a
	438: 14255172 439: 14255802	g C	a
	439: 14255802 440: 14258178	C	t
	441: 14259060	g	а
40	442: 14259161	C	t
40	443: 14265514	a	g
	444: 14266004	g	С
	445: 14266784	ā	g
	446: 14270911	С	t
45			
	447: 14271868	t	С
	448: 14273519	а	t
	449: 14275793	С	а
	450: 14275916	g	а
50	451: 14276093	t	С
	452: 14276177	a	g
	453: 14276528	g	a
	454: 14276897	g	a
	455: 14276972	t	C
55	456: 14278155	a	g
	457: 14278615	a ~	g a
	458: 14278692	g	a
	459: 14279892	g	a
	460: 14280148	g	u

	4.50.00001	_	~
	461: 14280291	a	g t
	462: 14280782 463: 14281042	c a	C
	464: 14283354	t	С
5	465: 14290678	t	С
· ·	466: 14290844	а	g
	467: 14295679	С	t
	468: 14297092	g	а
10	469: 14300848	t	c c
10	470: 14303184	t	g
	471: 14303913 472: 14303970	a g	a
	473: 14304669	C	g
	474: 14305073	t	Č
15	475: 14305360	t	С
	476: 14307893	t	С
11	477: 14308069	С	t
5	478: 14308329	a	С
	479: 14308625	t	C
₩ 20	480: 14309321	g	a
는 급 20 루 진	481: 14309465	g	c a
Π	482: 14310218	g	c
ũ	483: 14310672	t	g
 	484: 14311035 485: 14311228	a t	C
a 23	486: 14311491	g	a
2	487: 14311865	C	t
	488: 14312093	a	t
Li	489: 14312165	g	t
□ 30	490: 14312256	a	g
band band	491: 14312275	t	C
	492: 14312321	а	t
	493: 14312797	g	a
TU ac	494: 14313371	t	c t
35	495: 14313671 496: 14313711	C	a
	496: 14313711 497: 14315626	g C	ť
	498: 14317417	g	a
	499: 14317572	t	С
40	500: 14317812	С	g
	501: 14318978	t	a
	502: 14319024	а	g
	503: 14319433	g	a
4 ~	504: 14319634	g	a
45	505: 14319797	С	g
	506: 14320165	a C	g a
	507: 14320692 508: 14320813	c	t
	509: 14320844	t	g
50	510: 14321619	a	g
50	510. 113 5 1019		
	511: 14322052	а	g
	512: 14322154	а	g
	513: 14322220	а	g
55	514: 14323488	С	t
	515: 14323680	C	t
	516: 14323863	C +	a C
	517: 14323972 519: 14324040	t a	t
	518: 14324040	а	·

	519: 14325197 520: 14325540	a a	a a
	521: 14329541	t	C
	522: 14331105	С	t
5	523: 14338523	а	С
	524: 14339636	g	C
	525: 14340427	С	t
	526: 14348472	g	a t
10	527: 14350385	C	a
10	528: 14350727 529: 14351732	g t	g
	530: 14351732	g	ā
	531: 14352733	C	t
	532: 14353465	a	g
15	533: 14353545	t	С
	534: 14354282	t	a
Li	535: 14354993	t	C
n	536: 14355347	C	t a
	537: 14355495	C	a
를 20	538: 14356310 539: 14357040	g a	g
는 그 그 20 루 진 제	539: 14357040 540: 14357331	g	ā
1 W	541: 14359127	g	а
uj	542: 14363514	g	а
<u>⊨</u> 25	543: 14367075	C	t
빌	544: 14368787	g	t
: 0	545: 14373239	t	C
	546: 14373986	t	g g
H 20	547: 14375753	t	a
a 30	548: 14375760 549: 14375831	g a	C
	550: 14376454	c	g
는 30 식 디	551: 14376567	g	a
ΠJ	552: 14376808	t	а
35	553: 14377209	g	a
	554: 14377288	g	a
	555: 14377353	g	t a
	556: 14378276 557: 14378370	g	t
40		c a	g
40	558: 14379197 559: 14395036	a	c
	560: 14395259	g	a
	561: 14395598	ā	g
	562: 14395625	С	t
45	563: 14395690	t	g
	564: 14395722	t	C
	565: 14395818	g	C
	566: 14395870 567: 14395902	t a	t
50		g	a
30	569: 14396424	g	a
	570: 14397242	t	С
	571: 14397529	С	t
	572: 14398288	t	g
55	573: 14398896	g	C
	574: 14399028	С	t
	E7E. 142007E7	3	g
	575: 14399757 576: 14399925	a t	g
	576: 14399925	C	٠

		577: 14400367 578: 14400745	c g	a a
		579: 14401434	a ~	c a
	5	580: 14401454 581: 14402273	g C	a
	J	582: 14402935	t	C
		583: 14403897 584: 14405247	g C	c a
		584: 14405247 585: 14405732	C	t
	10	586: 14407060	а	t
		587: 14407160	t	c a
		588: 14412731 589: 14413737	c g	a
		590: 14414482	c	t
	15	591: 14414726	g	a
		592: 14417171 593: 14417396	t c	c a
<u></u>		593: 14417396 594: 14417433	g	t
		595: 14417477	c	t
	20	596: 14418160	C	t c
#= F1		597: 14419575 598: 14420742	t t	C
H		598: 14420742 599: 14421092	a	g
		600: 14421138	t	g
Y	25	601: 14422812	а	t
		602: 14424569 603: 14424712	g t	a g
		604: 14427528	g	a
		605: 14434249	a	g
	30	606: 14434697	g	a
		607: 14437186 608: 14437221	t t	g
ā		608: 14437221 609: 14438332	t	C
T		610: 14438364	t	
	35	611: 14438686	t	c a
		612: 14438954 613: 14439018	g t	6
		613: 14439018 614: 14439260	t	
		615: 14440001	С	t t
	40	616: 14443243	С	t
		617: 14446477 618: 14447783	c g	
		618: 14447783 619: 14447829	t	á
		620: 14448561	С	ç
	45	621: 14449993	С	ć
		622: 14453820 623: 14455156	a C	1
		623: 14455156 624: 14458430	g	i
		625: 14462774	ā	,
	50	626: 14464432	g	
		627: 14465972 628: 14466544	t a	
		628: 14466544 629: 14466865	a	
		630: 14477623	g	
	55	631: 14479073	t	
		632: 14479413	a	
		633: 14483845 634: 14484193	c t	
		635: 14485018	t	

		636: 14500633 637: 14501053 638: 14501214	a a g	g g t
	5	639: 14505546 640: 14507257 641: 14507719	c c a	t t g
	10	642: 14507822 643: 14508413 644: 14508697 645: 14509951	c a g c	g t a t
	15	646: 14511271 647: 14512196 648: 14513266 649: 14514848	c g t c	t a c t
 - 1	13	650: 14516734 651: 14517397 652: 14517691	c c t c	t t c t
	20	653: 14519222 654: 14519896 655: 14525005 656: 14528986	g g	t c c
H	25	657: 14529523 658: 14530483 659: 14531846 660: 14532854	g t c g	c a a
	30	661: 14534505 662: 14535097 663: 14539337 664: 14540886	а а с	a c a
		665: 14542312 666: 14545961 667: 14546904 668: 14546926	t g t g	c c a
1 127	35	669: 14549011 670: 14556845 671: 14558860 672: 14560480	g g a a	a t g
	40	673: 14561574 674: 14573065 675: 14574488	c a a t	t c c
	45	676: 14574929 677: 14581074 678: 14586576 679: 14588231 680: 14588677	g c g a	a Q t
	50	681: 14591087 682: 14594493 683: 14598453 684: 14600129	a c c	t 1 9
	50	685: 14601491 686: 14603502 687: 14603668	g t	i i
	55	688: 14609395 689: 14610858 690: 14615168 691: 14615291	t g t a	,
		692: 14616327 693: 14618602	g g	

	694: 14618604 695: 14618892 696: 14619088	g g	a t a
	697: 14621021	t	С
5	698: 14621080	a	g
5	699: 14621596	С	a
	700: 14626694	g	а
	701: 14627326	t	С
	702: 14627496	t	С
10			_
	703: 14627573	g	a
	704: 14627856	C	t
	705: 14628410	a	C
1.5	706: 14628606	t	c t
. 15	707: 14628943	g	g
	708: 14630897	a C	a
đ .	709: 14631416 710: 14631564	t	c
	710: 14631564 711: 14631874	C	g
⊒ 20	711: 14631674	C	ŧ
	713: 14633168	g	t
	714: 14633809	t	C
πi	715: 14635240	t	g
m	716: 14637360	a	g
20 	717: 14637499	a	t
	718: 14638334	а	g
1	719: 14638554	g	а
£ .	720: 14638696	t	С
	721: 14639083	g	a
<u></u> 30	722: 14639418	C	t
	723: 14639424	t	a
→ 30 → 30 → 30 → 30 → 30 → 30 → 30 → 31 → 35	724: 14640672	g	C C
ń	725: 14640709	g	c
ni os	726: 14640930	a	g
N 35	727: 14640953 728: 14641901	a a	g
	729: 14641976	g	ā
	730: 14642051	C	t
	731: 14642174	g	а
40	732: 14642247	t	а
	733: 14642286	a	g
	734: 14642392	t	C
	735: 14642614	С	t
	736: 14642775	a	c
45	737: 14642852	C	t
	738: 14644032	C	g t
	739: 14644292	C	a
	740: 14644589 741: 14644653	C	a
50		g C	ŧ
50	742: 14645037 743: 14645885	C	g
	744: 14646291	c	t
	745: 14646415	g	а
	746: 14647137	C	t
55	747: 14649329	g	а
	748: 14649396	t	С
	749: 14649442	g	a
	750: 14649469	а	g
	751: 14649532	a	С

19	757: 14650588 758: 14650730 759: 14650852 760: 14651277 761: 14651335 762: 14651435 763: 14651847 764: 14652004 765: 14652162	t c t t g a g g g a t c g c	CtCcagactgctat
1	5 766: 14652276	a	g
	771: 14654235 772: 14661002 773: 14662594 774: 14663947 775: 14664293 776: 14667946 777: 14668382 778: 14677906 779: 14677931	t c g t a a g a t a c a g	стасвравсвваг
17 C E	0 780: 14683355 781: 14683707 782: 14683953 783: 14685321 784: 14685566 785: 14685682 786: 14685868 787: 14686114 788: 14686396	a a g t g g a a t c	g g c c a a g g c t
2	789: 14686751 790: 14686876 791: 14687010 792: 14687213 793: 14689122 794: 14689887	c c g a t a	tatcc
	795: 14690010 796: 14690527 797: 14690707 798: 14693607 799: 14694039	g c t g t	a t c a c
	800: 14694137 801: 14694226 802: 14695601 803: 14697255 804: 14697625	t a a t t a	а а с с
	55 805: 14698201 806: 14702430 807: 14703794 808: 14707050 809: 14708403	a t g	g g a a

5	810: 14709040 811: 14713360 812: 14713782 813: 14715259 814: 14715324 815: 14715436 816: 14715840	0 + 0 + + 0 + 1	a c t g c t a a
10	817: 14716796 818: 14716938 819: 14717692 820: 14720670 821: 14720870	t a t a	a t g g
: 15 H	822: 14720958 823: 14721377 824: 14721393 825: 14723843 826: 14724043 827: 14724396 828: 14735736	a g c g c a c -	g t g c t g t a
급20 집	829: 14746369 830: 14747341	с g	t
如 户 ① 25	831: 14747564 832: 14749491 833: 14751000 834: 14752476 835: 14755501	t g g a g	c t a g a
0 H Q 30 V	836: 14757128 837: 14758013 838: 14760186 839: 14761259	a a a t a	t g g
3 5	840: 14761655 841: 14761848 842: 14762060 843: 14762610 844: 14763252	a c c c a t	g t t g
40	845: 14763339 846: 14763358 847: 14764385 848: 14764832 849: 14766118	c c c	t t 6
45	850: 14766695 851: 14767381 852: 14767448 853: 14767691 854: 14768282 855: 14768485	c c g g a a a	
50	856: 14769892 857: 14775735 858: 14778167 859: 14778548 860: 14780565	c g a g	
55	861: 14782481 862: 14783170 863: 14783238 864: 14783528 865: 14789648 866: 14789869 867: 14792310	c t g c g a a	

869: 14793358
871: 14794694 g a 872: 14795297 g c 873: 14795613 t g 874: 14800961 c t 875: 14801290 a g 876: 14806880 c t 10 877: 14806780 g t 878: 14808807 g a 879: 14812321 c t 880: 14815234 t g 881: 14815292 a g 15 882: 14826491 g a 883: 14827063 t g 884: 14827326 g a 885: 14827326 g a 886: 14828570 a t 887: 14830149 c t 889: 14830865 c a 890: 148373049 t t 891: 148373049 t g 893: 14839377 a g 894: 14839380 c g 897: 14844070 a g 899: 148440370 a g 899: 14
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	5	930: 14906025	t	g
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		932: 14907394	a	С
		933: 14907419	С	а
		934: 14907479	t	С
	10	935: 14907742	a	g
		936: 14916208	а	g
		937: 14916813	С	t
		938: 14916928	t	С
		939: 14917091	g	а
	15	940: 14917492	t	С
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		967: 14950617	С	t
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	45	969: 14957284	a	g
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	10		14970379 14970418	t		a
			14971526	g c		t
		996:	14971688	c		g
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			14973499	C		a
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	50	1032:	15012478	C		t
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		1034:	15013958	С		t
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		1041:	15019575	t		C

		1042:	15020203	t	С
		1043:	15020215	a	g
		1044:	15020761	C	t
		1045:	15021675	g	a
	5	1045:	15024870	a	C
	5	1040:	15027668	a	
		1047:	15027008	a	g t
			15020233	t	C
		1049:			t
	10	1050:	15030777	С	
	10	1051:	15031770	a	C
		1052:	15031862	a	g
		1053:	15032108	t	С
		1054:	15032579	g	a
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	25	1066:	15048235	g	а
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		1069:	15052308	g	С
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-	30	1071:	15052897	t	g
		1072:	15053077	С	t
		1073:	15053098	g	a
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	35	1076:	15053965	g	a
		1077:	15054237	t	g
		1078:	15054358	g	t
		1079:	15054369	ā	t
		1080:	15054413	а	g
	40	1081:	15054623	С	t
		1082:	15055285	а	g
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		1085:	15056524	С	g
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	55	1095:	15059704	g	c
	55	1096:	15061168	a	c
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	1148: 15112061	g	C
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	1150: 15113322	a	t
	1151: 15113753	t	С
	1152: 15113838	c	а
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10	1748: 15890995	g	t
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		1903: 16271911	a	g
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	35	2062: 16588769 2063: 16588795 2064: 16590838 2065: 16590876	t c c a	a g g
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	3	2093: 16650556	a	С
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		2095: 16655521	a	C
		2096: 16657891	t	C
	10	2097: 16662394	C	t
		2098: 16663696	t	g g
		2099: 16672093	a	g
		2100: 16673519 2101: 16676231	a a	t
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	15	2102: 16677194 2103: 16678005	C	t
		2104: 16681891	C	t
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		2106: 16682764	g	t
	20	2107: 16683603	С	t
		2108: 16684337	С	t t
===		2109: 16687109	С	t
IJ		2110: 16687553	С	C
	25	2111: 16698149	a	g
ļ.	23	2112: 16703153	c	t
J		2113: 16704088	g	t
E		2114: 16704721	g	а
m		2115: 16706524	С	t
	30	2116: 16712857	С	a
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-		2118: 16714465	t	c t
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	۰.	2120: 16719083	C	C
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		2123: 16722699	a	C
		2125: 16723138	a	g
	40	2126: 16724498	С	t
		2127: 16725584	С	t
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		2129: 16728578	С	g a
		2130: 16730217	g	g
	45	2131: 16731800 2132: 16733911	a C	t
		2132: 16733911 2133: 16735683	a	g
		2134: 16743342	a	g
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	50	2136: 16744767	a	g
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		2146: 16755168 2147: 16757712	g a	a g
		2148: 16759565	a	t c
	5	2149: 16760415 2150: 16761370	t a	g
	5	2151: 16761835	a	g
		2152: 16762035	g	a t
		2153: 16762736 2154: 16763708	a a	g
	10	2154: 16763708 2155: 16766281	g	t
	10	2156: 16768206	a	g
		2157: 16771694	t	g
		2158: 16774507 2159: 16774733	t a	g
	15	2159: 16774733 2160: 16775835	g	t
	15	2161: 16776519	a	g
		2162: 16777831	C	t C
hł		2163: 16779515 2164: 16782722	a a	g
	20	2164: 16782722 2165: 16783086	C	g
	20	2166: 16784610	a	g
		2167: 16784755	С	t
Ũ		2168: 16785179	a a	g
Ŋ	25	2169: 16785666 2170: 16785999	t	g
	23	2171: 16787543	c	t
Ū		2172: 16795739	t	C
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	30	2175: 16796880	С	t
		2176: 16796999	С	t
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	40	2183: 16802494	g	g
	40	2184: 16803878 2185: 16806306	c a	g
		2186: 16806336	C	t
		2187: 16807209	С	g
		2188: 16808583	a	g
	45	2189: 16808652 2190: 16808814	c c	t
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		2196: 16815577 2197: 16815841	a	Ģ
		2198: 16815843	g	(
	55	2199: 16816019	a	9
		2200: 16816059 2201: 16816317	a a	,
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		2203: 16818555	a	

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		2307: 16908351	c	t
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		2309: 16916913	а	g
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7		2525: 2526:	17218954 17219093	t t	c
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		2529:	17220847	t	C
		2530:	17222569	t	c a
	40	2531: 2532:	17223332 17223513	g C	t
	40	2532:	17223709	c	а
		2534:	17224579	C	t
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		2541:	17235409	а	g
	50	2542:	17237395	g	a
		2543:	17242185	C	t a
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		2545:	17248022	t	С
	55	2547:	17250853	С	t
		2548:	17256513	a	C
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		2612: 17310468	t		C
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		2617: 17315372	t		С
		2618: 17315412	g		t
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		2620: 17319817 2621: 17333207	a a		g
		2622: 17334125	c		g
	15	2623: 17335034	g		a a
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ļ.u		2626: 17336873	a		C
		2627: 17337652	g		а
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		2645: 17381259	C		a
		2646: 17381834	t		g
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		2649: 17383881 2650: 17383912	t a		g
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	10	2677: 17410475	a	g
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	50	2715: 17467646	g	
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		2719: 17473605	С	
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Ó			17676331	g	C
had the last the faith			17676441	g	a
r			17680205	g	а
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		2878: 3	17680484	t	С
		2879:	17680600	α	а
	40		17680841	g a	g
	40		17680997	a	g
			17681574	t	c
			17682962	С	g
			17683317	С	а
	45	2885:	17683766	C	а
		2886:	17684178	а	С
			17684698	t	g
			17684742	С	a
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	55	2896:	17694726	c	g
		2897:	17696863	c	a
		2898:	17698651	t	С
		2899:	17699827	C	a

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	45	2943: 17791361 2944: 17792413 2945: 17794602 2946: 17795187	a c t	g a c g
	50	2947: 17795652 2948: 17795980 2949: 17796086 2950: 17796688	a g t t	c a c
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		2958: 17803511	C	t
		2959: 17804498	a	a
		2960: 17810832	С	t
		2961: 17812485	С	t
	5	2962: 17819555	t	a
		2963: 17824538	t	C
		2964: 17828380	С	t
		2965: 17833406	а	g
		2966: 17833983	С	t
	10	2967: 17835269	t	С
		2968: 17836520	g	a
		2969: 17836781	С	g
		2970: 17841917	t	С
		2971: 17843934	t	C
	15	2972: 17844423	С	g
		2973: 17847113	a	g
		2974: 17850031	g	a
		2975: 17852052	С	g
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	20	2977: 17858294	а	C
Ξ		2978: 17864141	g	t ~
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		2984: 17885094	C	g C
		2985: 17887099	t	c
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	30	2987: 17902559	C	g
		2988: 17902569	a	a
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		2990: 17903104	g	t
n)	25	2991: 17903222	C +	a
	35	2992: 17903743	t t	c
		2993: 17903827	t	C
		2994: 17904859		a
		2995: 17905021 2996: 17905668	g a	t
	40		C	g
	40	2997: 17905975 2998: 17908674	g	t
		2999: 17909256	t	С
		3000: 17911473	C	а
		3000: 17911179	c	g
	45	3002: 17912462	t	g
	73	3003: 17912827	t	C
		3004: 17912924	С	t
		3005: 17913950	a	g
		3006: 17914144	t	С
	50			
		3007: 17915236	С	t
		3008: 17920938	g	а
		3009: 17921268	c	t
		3010: 17921350	t	С
	55	3011: 17921369	C	t
		3012: 17933425		t
		3013: 17935057		t
		3014: 17935888		t
		3015: 17937617	С	g

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				g
		a		t
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	3089: 18007737	С		t
		_		a C
				g
20				a
20				а
	3095: 18021524	а		С
		a		t
25				a C
25				a
				a
		c		t
	3102: 18064455	С		t
30	3103: 18064623	С		t
				g
				t t
	=			a
35				a
	3109: 18069198	t		С
		g		a
				a a
40				C
40				t
		a		С
	3116: 18074455	С		t
	3117: 18075694	g		a
45				g g
				a
				g
	- ·	a		g
50	3123: 18082352	С		t
	3124: 18083163	t		C
				t
				g t
55				g
55		t		С
	3130: 18087675	С		t
	3131: 18087828	g		t
	3132: 18087883	a		g
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	25	3155: 18142482 3156: 18142498 3157: 18143539 3158: 18144507 3159: 18146381	a g a g a	g a g a g
	30	3160: 18147285 3161: 18147368 3162: 18147479 3163: 18147849 3164: 18148090	a g t t a	g g g
IJ	35	3165: 18148391 3166: 18149727 3167: 18162515 3168: 18167850 3169: 18169299	g a c a	t t c t a
	40	3170: 18170395	g ,	Table 2
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	45	57: 14282614 58: 14289973 59: 14303801 60: 14305564 61: 14308745 62: 14309271	с д а д а	t t a g a
	50	63: 14313634 64: 14316517 65: 14336497	c t a	a C G C
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		74: 14368727	C	t
		75: 14380858	C	t g
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		79: 14450249	t	а
		80: 14523926	a	g
		81: 14529213	t	c a
	10	82: 14560271	g	a
		83: 14591293 84: 14601683	g t	C
		85: 14614643	t	C
		86: 14627536	C	а
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		88: 14639798	C	t c
		89: 14666163 90: 14686785	t c	t
		90: 14686785 91: 14778389	t ·	a
	20	92: 14791193	t	g
<u> </u>	20	93: 14806046	t	g
		94: 14808476	a	g
IJ		95: 14808794	g	a t
W.	25	96: 14809810 97: 14809974	C C	t
<u></u>	25	98: 14814482	g	a
Ф		99: 14814537	ť	а
£		100: 14823503	g	t
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	30	102: 14826425	g	a t
		103: 14827550 104: 14834456	c c	g
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Ŋ	35	107: 14890054	а	C
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		109: 14892649	С	t t
		110: 14900671 111: 14945268	a t	c
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		127: 15000928	g	C
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		130: 15001514	C	9

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		132: 15001785 133: 15001983	g a	g
		134: 15002044	C	t
	5	135: 15002118	t	C
		136: 15002260 137: 15002436	g g	C C
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		139: 15002601	a	g
	10	140: 15002681	a	g ~
		141: 15003106	C	g t
		142: 15003363 143: 15003544	g c	a
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	15	145: 15003973	g	t
		146: 15004000	C	t a
1 :		147: 15004200 148: 15004222	g t	g
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Ħ	20	150: 15004577	g	a
		151: 15004725	a	t c
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L	25	155: 15005084	g	а
ū		156: 15005148	a	g
±		157: 15005159	a	g a
		158: 15005540 159: 15025974	g t	C
طعا	30	160: 15026705	a	С
	50	161: 15048712	a	g
, J.		162: 15087229	g	a a
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N	35	164: 15141829 165: 15143231	g	a
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		173: 15351079 174: 15362167	a t	g
	45	174: 15362167 175: 15370212	a	g
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		182: 15414814	a	t
		183: 15423539	t	C
		184: 15424699	a +	t g
	55	185: 15427464 186: 15435332	t t	C
		186: 15435332 187: 15437951	a	g
		188: 15438194	t	C
		189: 15453738	а	С

		190: 15471061	t	С
		191: 15522640	a	С
		192: 15553225	a	g
	5	193: 15555505	С	t
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		195: 15617474	t	С
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		199: 15708909	t	c a
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		201: 15742331 202: 15745340	C	g
	15	202: 15745340 203: 15792778	C	t
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e _		206: 15814037	а	g
ja.		207: 15815872	g	а
	20	208: 15815917	t	C
		209: 15817984	t	C
		210: 15818374	a	g c
N		211: 15849570	a	t
Ø	25	212: 15857950 213: 15865992	a t	a
_	23	213: 15865992 214: 15881133	g	C
ű		215: 15887520	t	С
æ		216: 15895527	g	С
m		217: 15903809	а	t
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		225: 16029704	ā	g
		226: 16030927	t	C
		227: 16035195	а	Ĉ
	40	228: 16038904	g	t
		229: 16056870	C	
		230: 16094042 231: 16094737	t	<u>c</u> t
		231: 16094737	a C	t
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		235: 16171036	g	ć
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	55	243: 16327992 244: 16337850	g a	
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268: 16766335 c t	
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☐ 35 281: 16971929 a g ☐ 282: 17021105 g	
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,		316: 17276911 317: 17283143	g g	a
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		322: 17345540	g	t c
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		326: 17467870	t	С
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į.i	23	330: 17615441	g	С
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72

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		10: 13840293	С	a
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Ū		22: 13918743	g	а
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ū		24: 13939753	a	t
		25: 13954707	a	g
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	20	27: 13989194	t	g
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		49: 14141359	a	C
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	55	52: 14155080 53: 14201941	a t	g
	55	53: 14201941 54: 14203698	C	t
		55: 14203930	a	g
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		86: 14310283 87: 14312072	c a	g
123 123		87: 14312072 88: 14315594	t	c
7		89: 14325463	t	g
Fil	35	90: 14325687	g	t
14		91: 14336793	g	a a
		92: 14351418 93: 14351691	g g	C
		94: 14352181	C	t
	40	95: 14354527	t	С
		96: 14355445	С	g a
		97: 14361735 98: 14362906	g t	C
		98: 14362906 99: 14377173	t	C
	45	100: 14379074	a	C
		101: 14379466	C	t
		102: 14392496	t	c a
		103: 14392568 104: 14395584	g a	C
	50	104: 14395584 105: 14396231	C	t
	50	106: 14412774	а	g
		107: 14424801	t	C
		108: 14427417	t ·	C
	55	109: 14427482 110: 14440576	g c	a
	55	111: 14442675	t	g
		112: 14442719	t	g
		113: 14444533	a	g
		114: 14446001	а	g

5	115: 14448003 116: 14449153 117: 14454279 118: 14459068 119: 14464047 120: 14464959 121: 14465766 122: 14475385	t c t c a t t t	a t g t t c c c
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	30	199: 15014070 200: 15018850 201: 15020436 202: 15020440 203: 15056327	t g g a t	a a g
	35	204: 15064728 205: 15073139 206: 15078999 207: 15083283 208: 15115316	g t a c	a c c c
	40	209: 15115423 210: 15120676 211: 15123388 212: 15130427 213: 15137817	c g t a	g e t a a o t
	45	214: 15143098 215: 15143140 216: 15159625 217: 15160203 218: 15167150 219: 15174684	c c a c a t	t 6 9 1
	50	219: 15174684 220: 15183225 221: 15183636 222: 15224071 223: 15280085 224: 15281410	c a t t	1
	55	225: 15302421 226: 15328920 227: 15328921 228: 15329117 229: 15336885 230: 15340434	a a a g t	

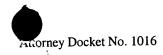
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		241: 15379111 242: 15381505	a t	g
		243: 15395614 244: 15418140	c t	g g
	15	245: 15427052 246: 15438583	a g	g t
		247: 15440219	a	g
		248: 15450658 249: 15469944	a t	g a
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	20	251: 15529113	a	g
		252: 15531290	g	t g
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		255: 15594759	C	t t
		256: 15599617 257: 15601332	c a	g
E		258: 15603328	c	g
	30	259: 15605767	а	g
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		281: 15707183	t	
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	55	284: 15716047 285: 15718727	a t	
		286: 15718927	g	
		287: 15721987	а	
		288: 15740761	С	

		000 15740761	C	t
		289: 15742761 290: 15743816	g C	a
		291: 15751207	a	g
		292: 15751246	a	t
	5	293: 15751359	С	t
		294: 15754104	t	c t
		295: 15760186 296: 15769673	c a	g
		296: 15769673 297: 15815282	c	ť
	10	298: 15817939	g	а
	10	299: 15833254	C	а
		300: 15835481	С	g
		301: 15851711	C	t g
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	15	303: 15853469 304: 15853824	a	g
		305: 15869264	t	С
		306: 15869845	t	a
ļ		307: 15870773	a	g
	20	308: 15872349	c t	g C
		309: 15896141 310: 15925924	t	c
		311: 16029732	t	C
200 E		312: 16030763	С	t
l U	25	313: 16033046	g	а
		314: 16044815	g	t t
F		315: 16059769	C	g
Ф		316: 16060265 317: 16063918	c c	ŧ
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		319: 16073916	g	a
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	35	322: 16093631 323: 16100689	c t	g
N		324: 16107592	t	g
		325: 16124106	a	g
		326: 16131138	t	C
	40	327: 16131244	С	a g
		328: 16134155 329: 16137958	a C	t
		330: 16139214	g	а
		331: 16140602	a	g
	45	332: 16140671	g	t
		333: 16140703	t	g t
		334: 16163942 335: 16167455	g	a
		335: 16167455 336: 16172690	g t	a
	50	337: 16184901	c	t
	50	338: 16185389	а	g
		339: 16187994	a	g
		340: 16293656	g	C
	<i>5 5</i>	341: 16305378 342: 16313571	a a	g g
	55	342: 16313571 343: 16336578	g	a
		344: 16360879	C	g
		345: 16423969	а	t
		346: 16423970	a	t

	347: 16423976	С		g
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10	356: 16544023	C		а
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15				a
13				g
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		t		а
	365: 16663333	g		а
20	366: 16704084	C		g
		a		t
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	375: 16791935	а		g
30	376: 16797023	а		C
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25				g
33	382: 16812750			g
	302. 10012/00			
	383: 16818812	t		a
	384: 16822411	а		t
40				t
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15		a		t
	392: 16886895	t		С
	393: 16930714	t		С
	394: 16943697	g		a
50				a
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55				a
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	403: 17119306	g		a
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	5	405: 17129588 406: 17131642 407: 17164499 408: 17165382 409: 17167672 410: 17174469 411: 17178186	a g a t a a a	c a g g t g
	10	412: 17180133 413: 17182569 414: 17186173 415: 17187712 416: 17193070	g t t g c	a c c a t
	15	417: 17193084 418: 17194501 419: 17209631 420: 17219055 421: 17220289	g c a a g	a t c a
	20	422: 17238397 423: 17244984 424: 17248128 425: 17257839 426: 17262723	a t g c c	g c a t g
	25	427: 17278114 428: 17281188 429: 17290111 430: 17316238 431: 17333820	t c g t t	c t a c c
	30	432: 17335050 433: 17343694 434: 17367747 435: 17369809 436: 17370858	t g t g	a a c t a
	35	437: 17373013 438: 17373879 439: 17375880 440: 17379865 441: 17384067	t a g t t	а с а
	40	442: 17393351 443: 17394036 444: 17396356 445: 17397743 446: 17398741	t a g g a	a g a a g
	45	447: 17402470 448: 17412963 449: 17437115 450: 17473474	c a a c	t g g t
	50	451: 17475236 452: 17480553 453: 17486157 454: 17501700 455: 17528110	t c t t t	ctcgc
	55	456: 17547768 457: 17550231 458: 17553702 459: 17570023 460: 17571585 461: 17580847 462: 17614190	g a g c t g c	a g c t a c t

		463: 17622058	t	C
		464: 17625750	С	t
		465: 17634579	a	g «
	_	466: 17639494	C	g t
	5	467: 17644090 468: 17647361	C C	t
		468: 17647361 469: 17650880	t	g
		470: 17651536	a	g
		471: 17660174	g	t
	10	472: 17660498	C	g
		473: 17663768	g	a -
		474: 17667391	C	t c
		475: 17668368	t t	C
	15	476: 17668835 477: 17693107	a	g
	15	478: 17694468	a	t
		479: 17760514	g	t
		480: 17761607	g	С
ļ.		481: 17771810	g	a
	20	482: 17773264	a	g
		483: 17794236	t	c a
I		484: 17794806	t	a
		485: 17801640 486: 17810038	g C	t
	25	487: 17823360	a	С
<u>L</u>	23	488: 17875449	t	С
Ü		489: 17900831	C	t
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n		491: 17903237	С	t t
	30	492: 17910169	C	C
2==#1		493: 17970301 494: 18001282	t t	g
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	35	497: 18011006	t	С
IJ		498: 18011472	С	t
		499: 18012518	a	g
		500: 18016807	a	g C
	40	501: 18017043	a t	C
	40	502: 18018684 503: 18020417	t	a
		504: 18021881	a	t
		505: 18024253	С	а
		506: 18025474	g	а
	45	507: 18030960	С	t
		508: 18031267	С	t
		509: 18067382	g	a t
		510: 18072464 511: 18073416	c a	g
	50	511: 18073416 512: 18078999	c	ť
	50	513: 18098017	g	t
		514: 18101558	а	g
		515: 18102008	a	C
		516: 18158420	g	a
	55			



It is to be understood that the above description is illustrative and not restrictive. The scope of the invention should, therefore, be determined not with respect to the above description, but instead with respect to the appended claims, along with the full scope of equivalents to which the claims are entitled.